NSAIDs

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ABSTRACT

INTRODUCTION: NSAIDs are widely used. Almost 10% of people in The Netherlands used a non-aspirin NSAID in 1987, and the overall use was 11 defined daily doses per 1000 population a day. In Australia in 1994, overall use was 35 defined daily doses per 1000 population a day, with 36% of the people receiving NSAIDs for osteoarthritis, 42% for sprain and strain or low back pain, and 4% for rheumatoid arthritis; 35% of the people receiving NSAIDs were aged over 60 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: Are there any important differences between oral NSAIDs? What are the effects of topical NSAIDs; and of co-treatments to reduce the risk of gastrointestinal adverse effects of oral NSAIDs? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 36 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the benefits and harms of the following interventions: differences in efficacy among different oral NSAIDs, between oral and topical NSAIDs, and between oral NSAIDs and alternative analgesics; dose–response relationship of oral NSAIDs; and H_2 blockers, misoprostol, or proton pump inhibitors to mitigate gastrointestinal adverse effects of oral NSAIDs.

QUESTIONS

INTERVENTIONS

Key points

- Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase (COX) enzyme to exert their anti-inflammatory, analgesic, and antipyretic effects.
- No important differences in efficacy have been demonstrated between different oral NSAIDs in the management of musculoskeletal disorders.

  There seems to be a plateau for effectiveness, with recommended doses close to those required for maximal effectiveness. However, the risk of adverse effects increases with increasing dose, with no plateau.

  Oral NSAIDs that selectively inhibit COX-2 have a reduced risk of causing gastrointestinal ulcers compared with less-selective NSAIDs. However, COX-2 inhibitors increase the risk of myocardial infarction and other cardiovascular events.

  Paracetamol is less effective than oral NSAIDs at reducing pain in osteoarthritis, but similarly effective for acute musculoskeletal pain.
- Misoprostol reduces serious NSAID-related gastrointestinal complications and symptomatic ulcers compared with placebo, but is itself associated with adverse effects including diarrhoea, abdominal pain, and nausea.

  Proton pump inhibitors and H_2 antagonists have been shown to reduce endoscopic ulcers in people taking NSAIDs, but their clinical benefits are less clear.

  We don't know which treatment is the most effective at reducing gastrointestinal adverse effects from oral NSAIDs.
- We don't know whether topical NSAIDs are beneficial.

DEFINITION

Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, analgesic, and antipyretic effects, and they inhibit platelet aggregation. This review deals specifically with the use of NSAIDs for the treatment of the symptoms of musculoskeletal conditions. NSAIDs have no documented effect on the course of musculoskeletal diseases. NSAIDs inhibit the enzyme cyclo-oxygenase (COX), which has two known isoforms: COX-1 and COX-2. NSAIDs are often categorised according to their ability to inhibit the individual isoforms, with newer NSAIDs often predominantly inhibiting the COX-2 isoform and older NSAIDs often being less specific inhibitors.

INCIDENCE/ PREVALENCE

NSAIDs are widely used. Almost 10% of people in The Netherlands used a non-aspirin NSAID in 1987, and the overall use was 11 defined daily doses per 1000 population a day. [1] In Australia in 1994, overall use was 35 defined daily doses per 1000 population a day, with 36% of the people receiving NSAIDs for osteoarthritis, 42% for sprain and strain or low back pain, and 4% for rheumatoid arthritis; 35% of the people receiving NSAIDs were aged over 60 years. [2]

AIMS OF INTERVENTION

To reduce symptoms in rheumatic disorders; to avoid severe gastrointestinal adverse effects.

OUTCOMES

Primary outcomes: pain intensity, including global efficacy scores; personal preference for one drug over another; clinically significant gastrointestinal complications. **Secondary outcomes:** number of tender joints; perforation; gastrointestinal haemorrhage; dyspepsia; and ulcer detected by routine endoscopy; other adverse effects.

METHODS

Clinical Evidence search and appraisal September 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2009, Embase 1980 to September 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs. We included systematic reviews of RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. For comparisons between paracetamol and an NSAID for musculoskeletal disorders, we included individual RCTs, as very few trials have been published. This review focuses on the use of NSAIDs for the treatment of the symptoms of musculoskeletal disorders. We have presented data regarding our primary outcomes in preference to data on secondary outcomes where available. More than 100 systematic reviews and thousands of RCTs have compared various NSAIDs. Owing to the large volume of data, in the question on different oral NSAIDs compared with each other, we assess NSAIDs for the indication of rheumatoid arthritis only as results in this population are generalisable to other musculoskeletal conditions. We assess the use of topical NSAIDs for any musculoskeletal condition. We have not included any systematic reviews that assess single NSAIDs — again, owing to the large volume of data. We have included systematic reviews and RCTs of the harms of NSAIDs (e.g., gastrointestinal toxicity) not solely in people with musculoskeletal disorders if the evidence would otherwise have been insufficient. Many RCTs are unpublished or published in sources not indexed in publicly available databases. The quality of the RCTs is variable and bias is common, both in the design and analysis of the RCTs, to such an extent that one systematic review identified false significant findings favouring new drugs over control drugs in 6% of RCTs. [3] We have favoured systematic reviews that have not been sponsored or authored by the pharmaceutical industry, because bias in such reviews has repeatedly been shown but may be difficult to detect. [4] For example, it is easy seemingly to follow the rules for systematic reviews and yet use inclusion and exclusion criteria that omit inconvenient studies. Furthermore, one systematic review found that industry-supported meta-analyses of drugs are of lower methodological quality, pay less attention to bias, and have fewer reservations than *Cochrane* reviews of the same drugs. [5] We have also favoured higher-quality reviews, based on search rigour and appropriate meta-analysis, over poorer-quality reviews with more-recent search dates. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent

only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). We believe that we have presented sufficient data to answer the question on the efficacy and safety of NSAIDs (both oral and topical) and that reporting further confirmatory data is not beneficial to our readers. We will continue to scan the literature, including drug safety monitoring, and will update the text of this review only should any high-quality evidence be published that reflects a change to the evidence we currently present.

QUESTION Are there any important differences among oral NSAIDs?

OPTION DIFFERENCES IN EFFICACY AMONG ORAL NSAIDS

Pain intensity

COX-2 inhibitors compared with older oral NSAIDs COX-2 inhibitors are as effective at reducing pain scores as older oral NSAIDs (high-quality evidence).

Other oral NSAIDs versus each other Different oral NSAIDs seem as effective as each other for pain relief in people with acute and chronic musculoskeletal disorders (high-quality evidence).

Oral NSAIDs compared with paracetamol NSAIDs may be no more effective than paracetamol at reducing pain in people with acute musculoskeletal disorders (high-quality evidence).

Gastrointestinal complications

COX-2 inhibitors compared with older oral NSAIDs COX-2 inhibitors, or COX-2-selective NSAIDs are associated with lower rates of symptomatic ulcers than older, non-selective NSAIDs (high-quality evidence).

Adverse effects (other than gastrointestinal)

Oral COX-2 inhibitors compared with older oral NSAIDs COX-2 inhibitors increase the risk of cardiovascular adverse events compared with placebo or older oral NSAIDs (high-quality evidence).

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits:

Oral indometacin (indomethacin) versus newer oral NSAIDs:
We found one systematic review (search date 1985, 37 crossover RCTs, 1416 people with rheumatoid arthritis), which compared indometacin versus 10 newer NSAIDs (naproxen in 8 cases) for a median of 2 weeks with each drug. [6] Four of the RCTs included a placebo period, and one RCT compared four drugs. The review found that 5% more people (95% CI 0% to 10%) preferred the newer NSAID to indometacin.

Oral cyclo-oxygenase-2 (COX-2) inhibitors versus older oral NSAIDs:
We found two systematic reviews (search dates 2002 [7] and 2000 [8]), which found that celecoxib and rofecoxib were no more effective for clinical outcomes than older NSAIDs in people with rheumatoid arthritis or osteoarthritis (see table 1, p 12). [7] [8] [9] [10] [11] Rofecoxib has been withdrawn from the market because of adverse effects (see harms below).

Other comparisons of oral NSAIDs versus each other:
We found five other systematic reviews comparing different oral NSAIDs. [12] [13] [14] [15] [16] The first of these systematic reviews (search date 1988, 88 RCTs, each comparing 2 NSAIDs, 6440 people with rheumatoid arthritis) found no significant differences in the number of tender joints improved between 17 different oral NSAIDs. [12] The second and third reviews (search dates 1994 [13] and 1996 [14]) found no clear differences between various oral NSAIDs used to treat osteoarthritis of the hip (39 RCTs) [13] or the knee (16 RCTs; see NSAIDs in review on osteoarthritis of the knee). [14] The fourth and fifth systematic reviews were in people with acute musculoskeletal syndromes and identified generally poor-quality RCTs. [15] [16] The fourth systematic review (search date 1993, 84 RCTs, 32,025 people with soft-tissue injuries of the ankle) was unable to meta-analyse data. [15] The fifth review (search date 1998, 17 RCTs for shoulder pain) was inconclusive. [16]

Oral NSAIDs versus oral paracetamol:
We found no systematic review but found two RCTs. [17] [18] The first RCT included 300 people with painful limb injuries. [17] People were randomised to four arms: daily intake for 3 days of paracetamol 4 g, diclofenac 75 mg, indometacin 75 mg, or paracetamol 4 g plus diclofenac 75 mg. The trial was double blind for the comparisons of paracetamol versus indometacin, and diclofenac versus paracetamol plus diclofenac. An imbalance in numbers in the four groups was caused by simple randomisation being used, rather than randomisation in blocks (Rainer TH, personal communication). It is therefore not an indication that the process was biased. The RCT found no significant or clinically relevant difference in pain reduction between the groups (on a 100-mm visual

analogue scale [VAS] [minimally relevant difference was 13 mm, based on other studies]; difference in pain reduction between indometacin and paracetamol: +5.7 mm, 95% CI –1.5 mm to +12.8 mm). In the second RCT (non-inferiority, 260 people with lateral ankle sprains), people were randomised to take either paracetamol 3.9 g or ibuprofen 1200 mg daily for 9 days. [18] The RCT found no significant difference in pain reduction on walking between the groups after 4 and 9 days (on a 100-mm VAS [0 = no pain; 100 = very severe pain]; day 4 mean change from baseline: –37 with paracetamol *v* –35 with ibuprofen; P = 0.24; day 9 mean change from baseline: –56 with paracetamol *v* –57 with ibuprofen; P = 0.73).

Harms:

Oral indometacin (indomethacin) versus newer oral NSAIDs:
The review that compared indometacin versus newer NSAIDs did not report on harms separately, but combined benefits and harms in one overall outcome (patient preference). [6]

Oral COX-2 inhibitors versus older oral NSAIDs:
We found two systematic reviews of the benefits and harms in people with rheumatoid arthritis or osteoarthritis; [7] [8] for harms see table 1, p 12 . We found three systematic reviews specifically on the harms of COX-2 inhibitors. [19] [20] [21] The first systematic review of harms (search date 2002) found that COX-2 inhibitors and older NSAIDs with substantial COX-2 inhibiting effects caused significantly lower rates of symptomatic ulcers compared with other older NSAIDs (COX-2 inhibitors *v* older NSAIDs: 17 RCTs, 25,564 people; RR 0.49, 95% CI 0.40 to 0.60; older NSAIDs with COX-2 inhibitory activity *v* other older NSAIDs: 51 RCTs, 28,178 people; RR 0.41, 95% CI 0.30 to 0.70). [19]

The second systematic review (search date 2004, 18 RCTs, 25,273 people) examined the risk of cardiovascular adverse events with rofecoxib in people with chronic musculoskeletal disorders. [20] It found that rofecoxib significantly increased the risk of myocardial infarction (MI) compared with placebo or older NSAIDs (RR 2.24, 95% CI 1.24 to 4.02). There was no evidence that results would differ according to comparator (P for interaction = 0.41). Rofecoxib was withdrawn from the market in 2004 after a placebo-controlled RCT found that it increased the risk of cardiovascular adverse effects. [22]

The third systematic review (search date 2005, 6 RCTs, 12,780 people) [21] looked at the cardiovascular adverse effects of celecoxib; one of the RCTs was misleadingly reported as it was not one RCT, but contained the combined results of two RCTs. [23] A meta-analysis of four of the RCTs (4422 people) found that celecoxib significantly increased the risk of MI compared with placebo (OR 2.26, 95% CI 1.00 to 5.10). When studies with diclofenac, ibuprofen, and paracetamol as comparators were included in the meta-analysis (total 6 RCTs,12,780 people), the review still found that celecoxib significantly increased the risk of MI (OR 1.88, 95% CI 1.15 to 3.08). [21] The available evidence suggests that the increase in MI is a class effect of the COX-2 inhibitors. [24]

Other comparisons of oral NSAIDs versus each other:
We found one systematic review (search date 2005,13 RCTs, 7718 people) of cardiovascular events with non-selective NSAIDs. [25] It found no significant difference in MI with non-selective NSAIDs compared with placebo (OR 1.3, 95% CI 0.8 to 2.1).

Oral NSAIDs versus oral paracetamol:
The RCT found that adverse effects occurred in less than 7% of cases and were not severe. [17]

Comment:

One of the RCTs identified by the review of the cardiovascular adverse effects of celecoxib, which compared celecoxib versus ibuprofen and diclofenac, has been criticised because the publication differs from the trial protocols in objectives, primary outcomes, statistical analysis, and trial duration. [7]

Clinical guide:
Important differences in adverse effects exist between different NSAIDs. The reduction in ulcers with COX-2 inhibitors should be weighed against the increase in cardiovascular risk compared with the older NSAIDs. [26] In contrast, the beneficial effects of NSAIDs seem similar. People's preferences for particular drugs have not been replicated and could therefore be due to chance or natural fluctuations in disease activity. [27] [28] The evidence suggests that, if the NSAID is unsatisfactory, then switching to another NSAID will not solve the problem. [27] [28] Likewise, doubling the dose of an NSAID leads to only a small increase in effect, which may not be clinically relevant, but results in increased adverse effects (see below). For acute musculoskeletal problems, it is doubtful whether NSAIDs have any clinically relevant anti-inflammatory effect; we found one large double-blind RCT comparing an NSAID versus paracetamol, which did not show any significant or clinically relevant differences, and another large RCT that did not find a significant difference in ankle swelling. [18] Paracetamol has been studied in osteoarthritis, where it had less effect than NSAIDs (see simple analgesics *v* NSAIDs in review on osteoarthritis of the knee).

OPTION DOSE–RESPONSE RELATIONSHIP OF ORAL NSAIDS

Pain intensity
High-dose compared with lower-dose oral NSAIDs High-dose oral NSAIDs have a very low benefit in terms of extra reduction in pain scores compared with moderate-dose NSAIDs (high-quality evidence). Recommended doses are close to creating the maximum benefit even in the low-dose range.

Adverse effects (other than gastrointestinal)
High-dose compared with lower-dose oral NSAIDs Adverse effects from NSAIDs increase in an approximately linear fashion with dose, with no ceiling (high-quality evidence).

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits: We found three systematic reviews. [12] [29] [30] The first review (search date 1985, 19 RCTs in which people were randomised to more than 1 dose of 9 different NSAIDs) found a dose–response relationship that saturated at high doses. [29] The differences in effect between the studied doses were very small or non-existent within the commonly used dose ranges (daily doses: phenylbutazone 50–300 mg, indometacin (indomethacin) 45–105 mg, ibuprofen 800–3200 mg, naproxen 250–1500 mg, piroxicam 10–30 mg, diclofenac 75–150 mg, diflunisal 500–1000 mg, and tolfenamic acid 300–600 mg); only for aspirin was there a difference (between 2.6 and 5.3 g) but this particular drug has never been recommended at the lower dose. [29] This and the second systematic review (search date 1992, 1545 people) [30] found that the recommended dosages were close to providing a ceiling effect. The third of these reviews (search date 1988, 115 RCTs) found no significant differences between various doses of drugs. [12]

Harms: Four systematic reviews (search dates 1992, [30] [31] 1994, [32] and 2001 [33]) found no ceiling effect for adverse effects, and found that the incidence of adverse effects increased in an approximately linear fashion with dose.

Comment: **Clinical guide:**
Doubling the dose of an NSAID leads to only a small increase in beneficial effect, which may not be clinically relevant, but it also doubles the risk of harms.

QUESTION What are the effects of co-treatments to reduce the risk of gastrointestinal adverse effects of oral NSAIDs?

OPTION MISOPROSTOL IN PEOPLE WHO CANNOT AVOID ORAL NSAIDS

Gastrointestinal complications
Misoprostol compared with placebo Misoprostol is more effective at reducing serious gastrointestinal complications and symptomatic ulcers (high-quality evidence).

Misoprostol compared with proton pump inhibitors We don't know how misoprostol and proton pump inhibitors compare at reducing gastrointestinal complications (low-quality evidence).

Adverse effects (other than gastrointestinal)
Misoprostol increases withdrawals caused by adverse events — mainly diarrhoea and abdominal pain — compared with placebo.

Note
We found no clinically important results from RCTs on the effects of misoprostol compared with H_2 blockers.

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits: **Misoprostol versus placebo:**
We found one systematic review (search date 2002, 23 RCTs) that reported on clinical outcomes. [19] It found that misoprostol significantly reduced serious gastrointestinal complications and symptomatic ulcers compared with placebo (serious gastrointestinal complications: 10 RCTs, 11,507 people; RR 0.6, 95% CI 0.4 to 0.9; symptomatic ulcers: 2 RCTs, 8913 people; RR 0.4, 95% CI 0.2 to 0.7).

Misoprostol versus proton pump inhibitor:
We found one systematic review (search date 2004), [34] which identified two fully published RCTs comparing misoprostol versus proton pump inhibitors. [35] [36] The first RCT in the review (935 people treated with NSAIDs who had ulcers or more than 10 erosions at endoscopy) compared misoprostol (200 micrograms 4 times daily) versus omeprazole (20 or 40 mg/day once daily). [35]

Treatment success was defined as fewer than five erosions at each site, no ulcers, and not more than mild dyspepsia. It found no significant difference in treatment success between misoprostol and omeprazole at 8 weeks (71% with misoprostol 800 micrograms *v* 76% with omeprazole 20 mg *v* 75% with omeprazole 40 mg; P greater than 0.2 for comparison of misoprostol *v* either dose of omeprazole). People having successful treatment (732 people) were re-randomised to receive maintenance treatment with misoprostol (200 micrograms twice daily), omeprazole (20 mg once daily), or placebo. Remission was defined as no ulcers, fewer than 11 gastric or duodenal erosions, only mild dyspepsia, and no adverse events requiring treatment discontinuation. Omeprazole significantly increased the proportion of people still in remission at 6 months compared with misoprostol (estimated AR: 48% with misoprostol *v* 61% with omeprazole; P = 0.001). The second RCT (537 people, using NSAIDs for at least 1 month and with a history of endoscopically confirmed gastric ulcer) compared four treatments: misoprostol (200 micrograms 4 times daily), two different doses of lansoprazole (15 and 30 mg) once daily, and placebo. [36] It found that misoprostol significantly increased the length of time to recurrence compared with the other treatments (time to gastric ulcer displayed graphically; misoprostol *v* placebo, P less than 0.001; misoprostol *v* lansoprazole 15 mg, P = 0.01; misoprostol *v* lansoprazole 30 mg, P = 0.04; AR for being free of gastric ulcer at 12 weeks: 93% with misoprostol *v* 80% with lansoprazole 15 mg *v* 82% with lansoprazole 30 mg *v* 51% with placebo).

Misoprostol versus H_2 blockers:
We found no systematic review of sufficient quality.

Harms:

Misoprostol versus placebo:
The review reporting on beneficial clinical outcomes did not report on the harms of misoprostol. [19] A second review (search date 2004) found that a significantly larger proportion of people receiving misoprostol than placebo withdrew because of adverse events, primarily diarrhoea, abdominal pain, and nausea (12 RCTs, 12,146 people; RR 1.41, 95% CI 1.31 to 1.51). [34] One large RCT (8843 people) identified by the review [34] found no significant difference in the proportion of deaths between groups (17/4404 [0.4%] with misoprostol *v* 21/4439 [0.5%] with placebo; ARR 0.10%; RR 0.82, 95% CI 0.43 to 1.55). One person taking placebo died as a direct result of gastrointestinal toxicity.

Misoprostol versus proton pump inhibitor:
The review found a significantly larger proportion of withdrawals with misoprostol than with proton pump inhibitors (RR 0.71, 95% CI 0.52 to 0.97). [34]

Misoprostol versus H_2 blockers:
We found no systematic review of sufficient quality.

Comment:

The clinical relevance of effects of co-treatments on endoscopically detected gastrointestinal ulceration is doubtful. The rate of ulcers was more than 10 times higher in the studies in which the investigators looked for ulcers with regular endoscopy than in earlier RCTs of NSAIDs, which looked for symptomatic ulcers. [37] The definition of ulcers varied between studies; sometimes they were defined as endoscopic lesions with a size of only 3 mm, sometimes as any lesion of an unequivocal depth, and sometimes no definition was provided at all.

Clinical guide:
Only misoprostol has been shown to reduce serious gastrointestinal complications and symptomatic ulcers compared with placebo, but this drug also causes people to withdraw from treatment because of gastrointestinal adverse effects.

OPTION H2 BLOCKERS IN PEOPLE WHO CANNOT AVOID ORAL NSAIDS

Gastrointestinal complications
Compared with placebo We don't know whether H_2 blockers are more effective than placebo at reducing gastrointestinal complications (low-quality evidence).

Compared with proton pump inhibitors H_2 blockers are less effective at reducing gastrointestinal complications of NSAIDs (moderate-quality evidence).

Note
We found no clinically important results from RCTs about the effects of H_2 blockers compared with misoprostol.

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits:

H_2 blockers versus placebo:
We found one systematic review (search date 2002, 15 RCTs, 2621 people) that reported on clinical outcomes. [19] It found insufficient evidence to compare the effects of H_2 blockers versus placebo on gastrointestinal complications or symptomatic ulcers reliably. However, it found that H_2 blockers significantly reduced endoscopically diagnosed ulcers compared with placebo (RR 0.6, 95% CI 0.4 to 0.7).

Proton pump inhibitors versus H_2 blockers:
We found one systematic review (search date 2004), [34] which identified one RCT (541 people with NSAID-related ulcers, or more than 10 gastric or duodenal erosions). [38] The RCT compared three treatments: omeprazole 20 mg, omeprazole 40 mg, and ranitidine 300 mg daily. Treatment success was defined as no ulcers, fewer than five erosions at each site, and only mild dyspepsia. It found that both doses of omeprazole significantly increased treatment success compared with ranitidine (80% with omeprazole 20 mg *v* 79% with omeprazole 40 mg *v* 63% with ranitidine; P less than or equal to 0.001 for comparison of ranitidine *v* either dose of omeprazole). People having successful treatment were re-randomised to either omeprazole 20 mg daily or ranitidine 300 mg daily. Relapse was defined as an ulcer, 10 or more gastric or duodenal erosions, moderate or severe dyspepsia, or treatment discontinuation caused by adverse events. Omeprazole significantly increased time to relapse compared with ranitidine (results displayed graphically; P = 0.004, log-rank test).

Misoprostol versus H_2 blockers:
We found no systematic review of sufficient quality.

Harms:

H_2 blockers versus placebo:
The review did not report on the harms of H_2 blockers. [19] Another systematic review (search date 2004) found no significant difference between low- or high-dose H_2 blockers and placebo in withdrawals caused by adverse effects (high dose: 1 RCT, 78 people; RR 1.00, 95% CI 0.21 to 4.65; low dose: 3 RCTs, 937 people; RR 0.86, 95% CI 0.58 to 1.28). [34]

Proton pump inhibitors versus H_2 blockers:
Few adverse events were reported in the RCT comparing omeprazole versus ranitidine. [38] Treatment discontinuations (all causes) occurred in 10% of people taking omeprazole 20 mg, 10% taking omeprazole 40 mg, and 14% taking ranitidine (significance not reported). [38]

Misoprostol versus H_2 blockers:
We found no systematic review of sufficient quality.

Comment: See comment on misoprostol in people who cannot avoid oral NSAIDs, p 5 .

OPTION PROTON PUMP INHIBITORS IN PEOPLE WHO CANNOT AVOID ORAL NSAIDS

Gastrointestinal complications
Compared with placebo We don't know whether proton pump inhibitors are more effective than placebo at reducing gastrointestinal complications (low-quality evidence).

Compared with H_2 blockers Proton pump inhibitors are more effective at reducing gastrointestinal complications of NSAIDs (moderate-quality evidence).

Compared with misoprostol We don't know how proton pump inhibitors and misoprostol compare at reducing gastrointestinal complications (low-quality evidence).

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits:

Proton pump inhibitors (PPIs) versus placebo:
We found two systematic reviews, one reporting on symptomatic ulcers and serious gastrointestinal complications, [19] and another examining endoscopic ulcers. [34] The first review (search date 2002, 6 RCTs, 1358 people) found too few serious gastrointestinal complications to compare the effects of PPIs versus placebo reliably. [19] Although initial analyses suggested a significant reduction in symptomatic ulcers with PPIs compared with placebo (2 RCTs, 343 people; RR 0.09, 95% CI 0.02 to 0.47), this significance was lost on sensitivity analysis, when the poor-quality study was removed from the analysis. The second review (search date 2004) identified five RCTs (1216 people) comparing PPIs versus placebo in people who had received NSAIDs for at least 3 months. [34] It found that PPIs reduced endoscopically diagnosed ulcers compared with placebo (RR 0.35, 95% CI 0.29 to 0.44).

PPIs versus H_2 blockers:
See benefits of H_2 blockers in people who cannot avoid oral NSAIDs, p 6 .

Misoprostol versus PPIs:
See benefits of misoprostol in people who cannot avoid oral NSAIDs, p 5 .

Harms:

Proton pump inhibitors (PPIs) versus placebo:
The review found no significant difference between PPIs and placebo in withdrawals caused by adverse effects (4 RCTs, 1113 people; RR 1.20, 95% CI 0.66 to 2.15). [34]

PPIs versus H_2 blockers:
See harms of H_2 blockers in people who cannot avoid oral NSAIDs, p 6 .

Misoprostol versus PPIs:
See harms of misoprostol in people who cannot avoid oral NSAIDs, p 5 .

Drug safety alert:
A drug safety alert has been issued on the possible increased risk of fractures of the hip, wrist, and spine, associated with the use of proton pump inhibitors. (www.fda.gov)

Comment:
See comment on misoprostol in people who cannot avoid oral NSAIDs, p 5 .

QUESTION What are the effects of topical NSAIDs?

OPTION NSAIDS (TOPICAL)

Pain intensity
Compared with placebo in people with acute musculoskeletal pain Topical NSAIDs may be more effective at reducing pain at 1 week in people with acute musculoskeletal pain, but the effect is small, at best (very low-quality evidence).

Compared with placebo in people with osteoarthritis Topical NSAIDs may be no more effective than placebo in people with chronic pain from osteoarthritis (very low-quality evidence).

For GRADE evaluation of NSAIDs, see table, p 13 .

Benefits:

We found three systematic reviews: one in people with acute musculoskeletal pain conditions [39] and two in people with osteoarthritis. [40] [41]

Topical NSAIDs versus placebo:
In people with acute musculoskeletal pain:
The systematic review in people with acute musculoskeletal pain (search date 2003, 36 RCTs) found that topical NSAIDs significantly improved "clinical success" rate compared with placebo at 1 week (26 RCTs, 2853 people; "clinical success" defined as "good" or "excellent" global assessment of treatment, or "none" or "slight" pain on rest or movement; AR for "clinical success": 65% with topical NSAIDs *v* 39% with placebo; RR 1.6, 95% CI 1.4 to 1.7; NNT 3.8, 95% CI 3.4 to 4.4; see comment below). [39] There was extreme statistical heterogeneity in this analysis (P less than 0.00001) (i.e., widely diverging results between trials), which means that these results should be interpreted with caution as they may not be reliable.

In people with osteoarthritis:
The first systematic review in people with osteoarthritis (search date 2003) found that, although topical NSAIDs significantly reduced pain compared with placebo at 2 weeks, this effect was not significant at 4 weeks (2 weeks: 6 RCTs, 893 people: effect size 0.40, 95% CI 0.15 to 0.65; P less than or equal to 0.05; 4 weeks: 3 RCTs, 558 people; effect size +0.04, 95% CI –0.11 to +0.19; P greater than 0.05; see comment below). [40] The analysis at 2 weeks was statistically heterogeneous (P less than 0.001).

The second systematic review in people with osteoarthritis (search date 2005, 8 RCTs, 6 included in the first review, 749 people receiving topical NSAIDs, number of people receiving placebo not reported) found that NSAIDs significantly improved pain compared with placebo at a mean 1.6 weeks (mean improvement of 12 mm, 95% CI 7 mm to 16 mm on a 100-mm visual analogue pain scale for NSAIDs *v* placebo; absolute numbers not reported; random effects model). [41] However, although this difference between groups was statistically significant, it was below what was deemed by the reviewers to reflect the average minimal clinically important improvement, namely 20 mm on a 100-mm visual analogue pain scale. This review also found heterogeneous results (P = 0.002 for test of heterogeneity) owing to the use of different topical NSAID gels over different time frames.

The reviews found only a single RCT comparing topical NSAIDs versus placebo for more than 4 weeks. [39] [40] [41]

Harms:

Topical NSAIDs versus placebo:
In people with acute musculoskeletal pain:
The review in people with acute musculoskeletal pain found no significant difference between topical NSAIDs and placebo in withdrawals caused by adverse effects (0.8% with topical NSAIDs *v* 0.7% with placebo; RR 1.6, 95% CI 0.8 to 3.4). [39]

In people with osteoarthritis:
The first review in people with osteoarthritis found no significant difference between topical NSAIDs and placebo in adverse events (crude rates: 108/577 [19%] with topical NSAIDs *v* 85/531 [16%] with placebo; RR 1.02, 95% CI 0.62 to 1.68). [40]

The second review in people with osteoarthritis gave no information on adverse effects. [41]

Comment:

All three reviews found that the effect decreased significantly and substantially with increasing sample size of the trials, rendering interpretation of the results difficult. [39] [40] [41] The trials identified by both reviews of NSAIDs for osteoarthritis were of poor quality, [40] [41] and this might also have been the case for the trials included in the review of acute pain conditions [42] (see published peer review comments on this review [39]).

OPTION TOPICAL VERSUS ORAL NSAIDS OR ALTERNATIVE ANALGESICS

Pain intensity
Topical NSAIDs compared with oral NSAIDs There may be no clinically relevant difference in pain reduction with topical NSAIDs compared with oral NSAIDs in people with acute and chronic pain (very low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of topical NSAIDs compared with paracetamol in people with musculoskeletal conditions.

For GRADE evaluation of NSAIDs, **see table, p 13 .**

Benefits:

We found two systematic reviews: one in people with acute musculoskeletal pain conditions (search date 2003, 36 RCTs) [39] and one in people with osteoarthritis (search date 2003, 13 RCTs). [40]

Topical NSAIDs versus oral NSAIDs:
The systematic review in people with acute musculoskeletal pain conditions found three RCTs (433 people), two of which compared the same NSAID delivered topically and orally. [39] The review found no significant difference between topical and oral NSAIDs in "clinical success" rate (AR: 57% with topical NSAIDs *v* 62% with oral NSAIDs; RR 0.9, 95% CI 0.8 to 1.1). The review did not specify length of follow-up in the RCTs identified.

The systematic review in people with osteoarthritis found two RCTs (529 people) that compared different NSAIDs given topically and orally. [40] The review found that topical NSAIDs were significantly less effective in reducing pain than oral NSAIDs at 1 week but not at 3 weeks (1 week: 1 RCT, 208 people; effect size –0.38, 95% CI –0.66 to –0.10; 3 weeks: 2 RCTs, 529 people; effect size –0.26, 95% CI –0.68 to +0.16).

Topical NSAIDs versus paracetamol:
We found no systematic review or RCTs.

Harms:

Topical NSAIDs versus oral NSAIDs:
We found no reliable RCTs comparing adverse effects of the same NSAID in topical and oral formulations. The review in people with acute pain conditions did not report on harms with topical NSAIDs compared with oral NSAIDs. [39] The review in people with osteoarthritis found that topical NSAIDs increased local adverse reactions compared with oral NSAIDs (crude rates: 18/243 [7%] with topical NSAIDs *v* 2/200 [1%] with oral NSAIDs; RR 5.3, 95% CI 1.1 to 24.5). [40]

Topical NSAIDs versus paracetamol:
We found no RCTs.

Comment:

Both reviews found that the effect decreased significantly and substantially with increasing sample size of the trials, rendering interpretation of the results difficult. [39] [40] The trials identified by the review of NSAIDs for osteoarthritis were of poor quality, [40] and this might also have been the case

for the trials included in the review of acute pain conditions [39] (see published peer review comments on this review). [42]

GLOSSARY

Defined daily dose The assumed average daily dose for the main indication of a specified drug. The defined daily dose per 1000 population a day is an estimate of the proportion of that population receiving treatment with that drug.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Topical NSAIDs versus placebo: One systematic review added [41] comparing topical NSAIDs versus placebo in people with osteoarthritis reached the same conclusions as previously cited review as it found many of the same RCTs. While topical NSAIDs reduce pain compared with placebo at 1 week, the pain reduction is likely to be clinically unimportant to patients. Categorisation unchanged (Unknown effectiveness).

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TABLE 1 **Cyclo-oxygenase-2 (COX-2) inhibitors versus older oral NSAIDs for the symptoms of musculoskeletal disorders.** [7] [8] [9] [10] [11]

Ref	Population characteristics	Interventions	Efficacy findings	Safety findings	Comments
RCT, [9] identified by systematic review [7]	1149 people with rheumatoid arthritis	Celecoxib 100, 200, and 400 mg, all twice daily *v* naproxen 500 mg twice daily	No significant difference between any dose of celecoxib and naproxen in improvement according to ACR 20 criteria 12 weeks: 50/235 (21%) with naproxen *v* 67/240 (28%) with celecoxib 100 mg *v* 50/235 (21%) with celecoxib 200 mg *v* 59/217 (27%) with celecoxib 400 mg RR 1.1, 95% CI 0.8 to 1.4 with celecoxib 100 mg RR 1.2, 95% CI 1.0 to 1.5 with celecoxib 200 mg RR 1.1, 95% CI 0.9 to 1.4 with celecoxib 400 mg	Celecoxib (100, 200, or 400 mg, all twice daily) significantly reduced endoscopically diagnosed gastrointestinal ulcers of at least 3 mm at 12 weeks compared with naproxen RR 0.2, 95% CI 0.1 to 0.5 with celecoxib 100 mg RR 0.2, 95% CI 0.1 to 0.4 with celecoxib 200 mg RR 0.2, 95% CI 0.1 to 0.5 with celecoxib 400 mg No significant difference between any dose of celecoxib and naproxen in clinical gastrointestinal adverse events or withdrawals due to gastrointestinal adverse events	Endoscopy results based on 560 people (61% of those randomised) who had endoscopy
RCT, [3] identified by systematic review [7]	655 people with rheumatoid arthritis	Celecoxib 200 mg twice daily *v* sustained-release diclofenac 75 mg twice daily	No significant difference between celecoxib and diclofenac in improvement according to ACR 20 criteria, pain, or participant and physician global assessment at 24 weeks Improvement by ACR 20 response: 80/326 (25%) with celecoxib *v* 73/329 (22%) with diclofenac; RR 1.1, 95% CI 0.8 to 1.5; other results presented graphically	Diclofenac significantly increased withdrawals due to gastrointestinal adverse events and increased endoscopically diagnosed gastroduodenal ulcers of at least 3 mm compared with celecoxib in the 430 people (66% of those randomised) who had endoscopy Withdrawals due to gastrointestinal events: 51/329 (16%) with diclofenac *v* 18/326 (6%) with celecoxib; RR 0.4, 95% CI 0.2 to 0.6 Ulcers: 33/212 (16%) with diclofenac *v* (4%) with celecoxib; RR 0.75, 95% CI 0.62 to 0.90	Endoscopy results based on 430 people (66% of those randomised) who had endoscopy
RCT, [11] identified by systematic review [7]	537 people with osteoarthritis or rheumatoid arthritis	Celecoxib 200 mg twice daily *v* naproxen 500 mg twice daily	No significant difference between celecoxib and naproxen in participant- or physician-rated global assessment at 12 weeks (both assessments scored from 1 = very good/asymptomatic to 5 = poor/severe/intolerable) Participant assessment: 2.9 at baseline to 2.5 at 12 weeks for celecoxib and naproxen; P = 0.809 Physician assessment: 2.9 at baseline to 2.4 at 12 weeks for celecoxib and naproxen; P = 0.997	Celecoxib significantly reduced endoscopically detected gastroduodenal ulcers at 12 weeks compared with naproxen: 9% with celecoxib *v* 41% with naproxen; P less than 0.001 No significant difference between celecoxib and naproxen in clinical gastrointestinal adverse events or withdrawal due to adverse events at 12 weeks Gastrointestinal adverse events: 92/269 (34%) with celecoxib *v* 107/267 (40%) with naproxen; P value not reported Withdrawal: 19/269 (7%) with celecoxib *v* 24/267 (9%) with naproxen; P value not reported	RCT has been criticised because the publication differs from the trial protocol in objectives, primary outcomes, statistical analysis, and trial duration
Systematic review (search date 2000, 1 RCT) [8]	8067 people with rheumatoid arthritis	Rofecoxib 50 mg *v* naproxen 500 mg twice daily	No significant difference between rofecoxib and naproxen in individual or investigator global assessment or function after a median of 9 months Improvement in individual's assessment: 12.8% with rofecoxib *v* 13.2% with naproxen; WMD –0.02, 95% CI –0.06 to +0.02 Improvement in investigator assessment: 12.3% with rofecoxib *v* 13.0% with naproxen; WMD –0.03, 95% CI –0.07 to +0.01 Improvement in function: 3.7% with rofecoxib *v* 4.0% with naproxen; WMD –0.01, 95% CI –0.03 to +0.01	Rofecoxib significantly reduced upper gastrointestinal events (perforations, ulcers, bleeds, or obstructions) compared with naproxen after median follow-up of 9 months Upper gastrointestinal events: 1.4% with rofecoxib *v* 3.0% with naproxen; RR 0.46, 95% CI 0.34 to 0.63 Rofecoxib significantly increased serious thrombotic cardiovascular events compared with naproxen: 45/4047 (1.11%) with rofecoxib *v* 19/4029 (0.47%) with naproxen; RR 2.36, 95% CI 1.38 to 4.02	

ARC 20 response: this represents a 20% improvement in tender and swollen joint counts plus a 20% improvement in 3 of the following 5 measures — patient and physician global assessment, pain, function, and an acute phase reactant; ref; reference.

TABLE **GRADE evaluation of NSAIDs.**

Important outcomes	**Pain intensity, gastrointestinal complications, other adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
Are there any important differences between oral NSAIDs?									
4 (10,408) [3] [8] [9] [11]	Pain intensity	COX-2 inhibitors *v* older oral NSAIDs	4	0	0	0	0	High	
244 (at least 38,465 people) [12] [13] [14] [15] [16]	Pain intensity	Different oral NSAIDs *v* each other	4	0	0	0	0	High	
2 (560) [17] [18]	Pain intensity	Oral NSAIDs *v* paracetamol	4	0	0	0	0	High	
68 (53,742) [19]	Gastrointestinal complications	COX-2 inhibitors *v* older oral NSAIDs	4	0	0	0	+1	High	Effect-size point added for RR less than 0.5
24 (38,053) [23] [21]	Cardiovascular adverse events	COX-2 inhibitor *v* older oral NSAIDs	4	0	0	0	0	High	
At least 115 RCTs, at least 1545 people [12] [29] [30]	Pain intensity	High-dose *v* lower-dose oral NSAIDs	4	0	0	0	0	High	
4 reviews (at least 1545 people) [30] [31] [32] [33]	Adverse effects (other than gastrointestinal)	High-dose *v* lower-dose oral NSAIDs	4	0	0	0	0	High	
What are the effects of co-treatments to reduce the risk of gastrointestinal adverse effects of oral NSAIDs?									
10 (11,507) [19]	Gastrointestinal complications	Misoprostol *v* placebo	4	0	0	0	0	High	
2 (1472) [35] [36]	Gastrointestinal complications	Misoprostol *v* proton pump inhibitor	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of ulcers detected endoscopically
15 (2621) [19]	Gastrointestinal complications	H_2 blockers *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of ulcers detected endoscopically
1 (541) [38]	Gastrointestinal complications	H_2 blockers *v* proton pump inhibitors	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of ulcers detected endoscopically
6 (1358) [19]	Gastrointestinal complications	Proton pump inhibitors *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for different results with sensitivity analysis. Directness point deducted for inclusion of ulcers detected endoscopically
What are the effects of topical NSAIDs?									
26 (2853) [39]	Pain intensity	Topical NSAIDs *v* placebo for any acute musculoskeletal pain	4	–1	0	–2	0	Very low	Consistency point deducted for extreme heterogeneity of trials analysed. Directness points deducted for unclear outcome measure and very short-term follow-up

Important outcomes	Pain intensity, gastrointestinal complications, other adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
8 (1141) [40] [41]	Pain intensity	Topical NSAIDs *v* placebo for osteoarthritis	4	–1	–1	–1	0	Very low	Quality point deducted for methodological problems with some studies. Consistency point deducted for heterogeneity of trials in meta-analyses. Directness point deducted for no long-term outcome data
5 (962) [39] [40]	Pain intensity	Topical NSAID *v* oral NSAID	4	–1	–1	–1	0	Very low	Quality point deducted for poor-quality of included RCTs. Consistency point deducted deducted for heterogeneity of trials in meta-analyses. Directness point deducted for no long-term outcome data

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.